GINGIVAL ENLARGEMENT IN EPILEPTIC PATIENTS ON PHENYTOIN THERAPY-AN OVERVIEW OF POSSIBLE ETIOLOGIES AND STUDIES

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Abstract

Epilepsy is a common neurological disorder with recurrent seizures due to a chronic underlying process. Despite tremendous advances in the field of understanding regarding the etio-pathogenesis of epilepsy, phenytoin still remains the drug of choice in its management. Chronic administration of phenytoin has been associated to have a number of adverse effects. Gingival enlargement is one such most often reported adverse drug sequela of long term phenytoin usage with exclusion of local factors contributing towards gingival enlargement. This review gives an overview regarding the association of phenytoin and gingival enlargement seen in epileptic patients being treated with phenytoin.

Key Words: Epilepsy, gingival enlargement, phenytoin.

Introduction

Introduction - Epilepsy is described as a chronic neurological disorder characterized by recurrent seizures of cerebral origin, presenting with episodes of sensory, motor or, autonomic phenomenon with or, without loss of consciousness. [1] A recent meta-analysis of published and unpublished studies puts an overall prevalence rate of epilepsy in India at 5.59 per 1,000 populations. [2] Despite the tremendous advances in the management of epilepsy, phenytoin still remains the drug of choice; however, the long term administration of phenytoin has been seen to lead to a number of adverse effects. Gingival enlargement is one such most frequently reported adverse drug effect of phenytoin. [3] Approximately 40-50% of the patients treated with phenytoin develop esthetically disfiguring enlargement of the gingivae. Whenever occurs, this adverse effect of phenytoin, lasts throughout the period of therapy and continues further with a severe reduction in the quality of life of the affected individual. The pseudo-pockets that are formed as a result of gingival enlargement increase plaque retentive areas which further predispose the patient towards an enhanced susceptibility for super-added inflammatory changes in the gingivae, dental caries and periodontal disease. [4, 5] However, the etio-pathogenesis of phenytoin induced gingival enlargement is still not clearly understood. A number of studies however indicate its multi-factorial etiology including oral hygiene status of the affected epileptic patients. [6] The present review gives an overview regarding the association of phenytoin and gingival enlargement seen in epileptic patients being treated with the drug, excluding the role of local factors, if any, that could lead to secondary inflammatory changes.

Discussion

Despite tremendous advances in the management of epilepsy in the last decade, the anti-epileptic drug phenytoin still remains the prime drug of choice in the management

of epileptic patients in India. [7, 8] Chronic administration of phenytoin has been associated with a number of adverse effects. [9, 10] Gingival enlargement is one such most often reported adverse drug consequence of long term phenytoin usage. [11]

Numerous reports suggest that phenytoin induced gingival enlargement is more commonly seen in younger age groups. This is in concordance with the observations of the several epidemiological studies conducted by Steinberg and Steinberg, 1982, Stinnett et al, 1987, Dahllof and Modeer, 1986, and Thomason et al, 1992. Also, both genders have been reported to be equally susceptible to phenytoin induced gingival enlargement in the literature. [11] The incidence of phenytoin induced gingival enlargement as reported by a study conducted by Kimball was found to be 57% while other studies conducted in relation to incidence of phenytoin induced gingival enlargement have revealed wide incidence ranges from somewhere around 20-40 % [12, 13] in some studies to 6-79 % in others [13-18] and in fact in 3-93% in few other studies [19, 20]. The incidence of phenytoin induced gingival enlargement has been found to be 50% in institutionalized epileptic patients (Seymour, 1993) as reported in the literature. Gingival enlargement has also been seen in normal, healthy adults. The incidence of gingival enlargement in the normal population has been reported to be between 4-7.5%. [21] This wide range of variability may be attributed to the small number of the cases reported in some publications, to large variations in phenytoin dosages, to monotherapy and polytherapy, to variations in the length of phenytoin exposure, and to differences in the age of the patients included in the various studies that is related to the connective tissue viability and reactionary enlargement seen in such individuals secondary to drug exposure as well.

Phenytoin induced gingival enlargement normally begins at the interdental papillae and is more frequently found in the anterior segments of the jaws though it often involves all the surfaces of teeth and is generalized in its distribution. [9, 17, 18] Gradually, gingival lobulations are formed that may appear inflamed or, more fibrotic in nature depending on the degree of local factors' induced secondary inflammatory changes. The patients although are not subjected to surgical therapeutic options for the treatment as this therapeutic option has often been seen to carry a high probability for recurrence. [8, 9, 11]

Numerous studies conducted in the past have correlated this phenytoin induced gingival enlargement to a number of the possible causative factors. A comprehensive review of the literature also proposes a plethora of the possible etiologies for phenytoin induced gingival enlargement. Although till today, the exact role inflammatory changes could play or, even before that, the possible etiological factors that could trigger this reactionary process and lead to massive gingival enlargements, has remained unclear. This review focuses on the more common etiologies proposed behind phenytoin induced gingival enlargement which have received widespread acceptance.

Drug-Induced Gingival Enlargement:

Drug-induced enlargement has been associated with a patient's genetic predisposition. [9] Some investigators assert that underlying inflammation is necessary for the development of drug-induced enlargement [10], while others purport that the existing enlargement induced by the drug effect compounds plaque retention, thus furthering the tissue response. [22]

Gingival enlargement is associated with multiple factors including inflammatory (acute and chronic), idiopathic, drug-induced, neoplasia (benign and malignant tumors), hormonal disturbances, ascorbic acid (vitamin C) deficiency and with dental eruption. Phenytoin induced gingival enlargement is one of the most commonly reported gingival enlargement seen in the

category of drug-induced gingival enlargements. [11]

Currently, more than 15 drugs, including oral contraceptives, have been identified as possible causative agents for drug-induced gingival enlargements. [8, 23]

However, there are three established classes of drugs that are held responsible for leading to drug-induced gingival enlargements and these include anti-epileptics, anti-hypertensives, primarily calcium antagonists and immunosuppressant cyclosporine. One property that is common to these three classes of drugs is that they all directly affect cellular calcium metabolism. Since cellular production of collagenase is modulated by calcium influx, fibroblasts from patients treated with these drugs may produce an inactive form of collagenase, being responsible for an increase in extra-cellular matrix. [11]

The precise mechanism by which drug-induced gingival enlargement occurs however is still not completely understood, although a number of hypotheses have been suggested. [6] Phenytoin probably is proposed to interact with a sub-type of susceptible fibroblasts, cyclosporine is hypothesized to affect the metabolism of these cells and nifedipine is said to enhance this effect reducing their metabolism. [8, 24] Several factors may influence the relationship between the various implicated drugs and components of the gingival tissues, including: age, genetic predisposition, pharmacokinetic variables, drug-induced alterations in gingival connective tissue homeostasis, ultra-structural factors and inflammatory changes and drug-induced action on growth factors, etc. Three significant factors which are considered to be the most important etiological factors in the expression of these gingival changes include: drug variables, plaque-induced inflammatory changes in the gingival tissues and genetic factors, the latter determining the heterogeneity of the gingival fibroblasts, making the effect to be seen with more severity in specific set of patients. [25]

Also, some drugs induce a direct effect on a sub-group of fibroblasts, named "responders", that are apparently genetically determined to be sensitive to the drug causing gingival overgrowth. Such drugs produce a decrease in calcium influx (due to alterations in calcium-sodium exchange), which causes a decrease in cellular folic acid uptake (producing a localized folate deficiency) thus, limiting the production of the collagenase-activating enzyme, leading to the accumulation of redundant connective tissue. Also, since the presence of inflammation secondary to dental plaque causes proliferative increases in connective tissue, the catabolic ability of collagenase is saturated, and the inhibited degradation of the extra cellular matrix causes a local accumulation of this matrix. [4, 11] Not to end here, several other factors have been held responsible for drug-induced gingival enlargement, including the so-named androgenic hormones. [26]

Brown et al (1991) have pointed out in this entity several factors including increase of sulphatid glicosamines, immunoglobulins and epithelial growth factor, a decrease in calcium influx (due to alterations in calcium-sodium exchange) in fibroblasts and a tissue-level folic acid and collagenase deficiency to be responsible for drug-induced gingival enlargement. [4] Saito et al (1996) have shown an increase in basic fibroblast growth factor and expression of its receptors and glicosaminoglicans and heparan sulphate to be involved in gingival enlargement caused by phenytoin and nifedipine by immunohistochemistry studies. This has been later confirmed in various other studies. [27, 28]

The clinical presentation of the specific enlargement and the inflamed tissues is associated with specific macrophagic phenotypic picture that express beta- citocine IL-1 in tissues or, platelet derived growth factor. Iacopino et al (1997) and Saito et al (1999) have speculated that p53 protein expression in drug-induced gingival enlargement suggests that its pathogenesis is involved with DNA abnormalities. [29, 30]

Reductions of salivary IgA levels as well as an alteration of sub-gingival microflora have also been accounted to be causative of gingival enlargement induced by phenytoin but have not been confirmed in the later work. [31-5]

Dose-dependent correlations with the severity of gingival enlargements have been however weak, but decreased drug use, in general, has been seen to lead to reduced severity of gingival pathology. For example, phenytoin was reported to effuse into crevicular fluid without any correlation to the incidence of gingival overgrowth (McLaughlin *et al*, 1995), while no direct link was shown between overgrowth and the concentrations of phenytoin and metabolites (Ball *et al*, 1996). A more recent work supported a correlation between diminished metabolism of phenytoin in affected individuals and gingival overgrowth (Kamali *et al*, 1999), but this has not been confirmed. Age, gender, concomitant drugs, local factors such as plaque accumulation, and genetic predisposition have been cited as additional complicating risk factors in drug-induced gingival enlargements (Thomason *et al*, 1995, 1996; Cebeci *et al*, 1996).

Treatment of the gingival overgrowth lesion itself could be complicated due to the superimposed inflammatory changes. Traditionally, periodontal therapy offered removal of the inflammatory component of the overgrowth through scaling and gingival curettage, followed by excision of the overgrown gingiva (Kimball, 1939; Hassell and Hefti, 1991). [36, 37] For patients with severe gingival overgrowth and who require continuous drug therapy for medical reasons, gingivectomy might have to be repeated periodically due to the recurrent nature of drug-induced gingival overgrowth (Hall, 1997; Ilgenli *et al*, 1999; Kantarci *et al*, 1999).

Also, in drug-induced gingival enlargements, reversing and preventing gingival enlargement is as easy as ceasing drug therapy. However, this is not always feasible; in such a situation, alternative drug therapy might be employed, if possible, to avoid this deleterious side effect. In the case of immuno-suppression, tacrolimus is an available alternative which results in much less gingival overgrowth than cyclosporin, but is similarly as nephrotoxic. [38] The dihydropyridine derivative isradipidine can replace nifedipine for some uses of calcium channel blocking and has not been seen to induce gingival overgrowth. [39]

Phenytoin and Gingival Enlargement: Review of Different Studies: In a study published in 1976 in the Proc Natl Acad Sci by Hassell TM, Page RC, Narayanan AS, Cooper CG [40] titled Diphenylhydantoin (Dilantin) gingival hyperplasia: Drug-induced abnormality of connective tissue, it was found that the tissue overgrowth was made up predominantly of collagen and may therefore serve as a useful model for analysis of fibrosis and some other connective tissue abnormalities. Fibroblasts derived from the overgrown tissue exhibited a level of protein synthetic activity that was found to be approximately twice that of comparable cells obtained from non-epileptic control individuals and from the gingivae of age matched epileptics taking the drug but not exhibiting gingival enlargement. In addition, 20% of the protein synthesized by the cells from the overgrown tissue was found to be collagen while collagen was found to account for only about 11% of the total protein produced by the control cells of both types. The drug appeared to induce or, select for fibroblasts characterized by enhanced levels of protein synthesis and collagen production. This alteration was seen to persist through several cell replications in-vitro in the absence of drug later.

In an in-vitro study of protein and collagen synthesis by diploid fibroblasts from seventeen non-epileptic young individuals with healthy gingivae published in 1983 in the Am J Pathol based on phenytoin sensitivity of fibroblasts as the basis for susceptibility to gingival enlargement by Hassell TM, Gilbert GH [41], only seven strains of cells responded to phenytoin in culture medium. Because not

all phenytoin-treated individuals develop gingival overgrowth, it was suggested that susceptibility is predicated upon the presence of a (genetically determined) phenytoin-sensitive sub-population of gingival fibroblasts. The concept of the participation of sensitive cell sub-populations in other connective tissue disorders was also supported by these findings.

In a study published in 1993 in the Federation of European Biochemical Societies by Shikata Hideo, Utsumi Nobuo, Shimojima Takahiro, Oda Yoshio, Okada Yasunori [42] on increased expression of type VI collagen genes in drug-induced gingival enlargement, fibrotic gingival enlargements induced by phenytoin or, nifedipine were examined with special reference to type VI collagen expression. Immuno-localization studies showed abnormal accumulation of type VI collagen around the collagen fiber bundles in the fibrotic gingival enlargements. Examination of total RNA extracted from fibroblasts and tissues of enlarged gingivae demonstrated increased type VI collagen steady-state mRNA levels. These results suggested that excessive deposition of type VI collagen in drug-induced gingival enlargement is attributed to increased expression of the collagen genes.

In a study published in 1995 in the Journal of Therapeutic Drug Monitoring conducted by Perlik F, Kolinova M, Zvarova J, Patzelova V [43] on phenytoin as a risk factor in gingival hyperplasia, fifty-four out-patients with epilepsy who had been taking phenytoin for more than one year were examined for gingival hyperplasia. Approximately 76% of patients showed either mild or, no gingival hyperplasia. Lesion severity was then compared statistically to phenytoin dosage and drug concentrations as well as to other clinical and laboratory parameters. There was seen a tendency for gingival hypertrophy to be associated with both increasing dosage of phenytoin per unit of body weight and the duration of phenytoin administration. All patients followed had a statistically significant progressive trend to increasing gingival hyperplasia with higher total and free phenytoin concentration.

In a cross-sectional study published in 2001 in the European Journal of Clinical Investigation by Brunet L, Miranda J, Roset P, Berini L, Farre M, and Mendieta C [44] on the prevalence and risk of gingival enlargement in patients treated with anti-convulsant drugs, data from fifty nine patients taking anti-epileptics were compared with ninety eight controls. Gingival enlargement was evaluated with two indices to score vertical overgrowth [Gingival overgrowth index, (GO] and horizontal overgrowth [Miranda-Brunet index, (MB)]. Gingival index, plaque index, and probing depth were also evaluated. This study was conducted with an aim to determine, with the aid of two indices that score vertical and horizontal overgrowth, the prevalence and risk factors for gingival enlargement in patients treated with phenytoin and other anti-convulsant drugs. The study revealed that the prevalence of gingival enlargement was significantly higher ($P < 0{\cdot}0001$) for both indices in the anti-convulsants treated groups than in the control group. Gingival overgrowth was also found to be significantly higher for both indices in the phenytoin group than in the non-phenytoin group. Among the possible risk factors, only the gingival index showed a significant association with gingival enlargement. For the MB index, the risk of gingival enlargement (odds ratio) associated to phenytoin therapy and other anti-convulsants therapy were 52·6 (13·5–205) and 6·6 (1·5–28·2). Gingival index-adjusted odds ratios for the same drugs were 5·7 (1·3–24·7) and 18·1 (2–158), respectively. The concordance between GO and MB indices in the control group and in the phenytoin-group and non-phenytoin-group showed a Kappa value of 0·773 and 0·697, respectively. The study concluded with significant differences in the prevalence and severity of gingival overgrowth in two groups of patients, one treated with phenytoin, and another treated with other anti-convulsant

drugs. Gingival inflammation was held a significant risk factor for gingival enlargement in these patients.

In two case reports published in 2004 by Marakoglu Ismail, Gursoy Ulvi Kahraman, Cakmak Hulya, Marakoglu Kamile [45] in Yonsei Medical Journal titled phenytoin induced gingival overgrowth in un-cooperative epilepsy patients; the problem of un-cooperative epilepsy patients was highlighted as being one of the most unsuccessfully treated periodontal patient groups because of the difficulty in maintaining their oral hygiene.

Conclusion

The results of the studies conducted in the past suggest a higher incidence and severity of drug-induced gingival enlargement in phenytoin treated epileptic patients with local factors having a little role, if any, towards phenytoin induced gingival enlargements. A direct correlation with an increased incidence and severity at higher dosages, and the role of local factors in confounding and worsening the drug-induced gingival overgrowths have however remained debatable despite support from some studies. The present review bringsforth the possible etiologies behind phenytoin induced gingival enlargements. However, further research is required to analyze the exact etiology behind these types of drug-induced gingival enlargements possibly by subjecting the tissues affected for a detailed histo-pathological analysis as the patients usually are not subjected to surgical therapeutic options for the treatment since they have been seen to carry a high probability for recurrence. The review encourages further research to confirm the histology of phenytoin induced gingival enlargements to find out the most feasible therapeutic options to overcome this inadvertent adverse sequel of long term phenytoin administration required for the management of patients suffering from this chronic disease.

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